STAT3 gene

signal transducer and activator of transcription 3

Normal Function

The *STAT3* gene is part of a family known as the STAT genes. These genes provide instructions for making proteins that are part of essential chemical signaling pathways within cells. When STAT proteins are activated by certain chemical signals, they move into the nucleus and attach (bind) to specific areas of DNA. By binding to regulatory regions near genes, STAT proteins can regulate whether these genes are turned on or off. STAT proteins are called transcription factors on the basis of this action.

The STAT3 protein is involved in many cellular functions. It regulates genes that are involved in cell growth and division, cell movement, and the self-destruction of cells (apoptosis). The STAT3 protein is active in tissues throughout the body. It plays an important role in the development and function of several body systems and is essential for life. In the immune system, the STAT3 protein transmits signals for the maturation of immune system cells, especially T cells and B cells. These cells help control the body's response to foreign invaders such as bacteria and fungi. In addition, the protein is involved in the regulation of inflammation, which is one way the immune system responds to infection or injury. In the skeletal system, the STAT3 protein is involved in the formation of specialized cells that build and break down bone tissue. These cells are necessary for the normal development and maintenance of bones.

Health Conditions Related to Genetic Changes

autosomal dominant hyper-IgE syndrome

More than 100 germline mutations in the *STAT3* gene have been identified in people with autosomal dominant hyper-IgE syndrome (AD-HIES), a disorder of the immune system that leads to recurrent skin and lung infections as well as abnormalities of the bones and teeth. Most of the mutations involved in this condition change single amino acids in the STAT3 protein. These mutations occur in regions of the protein that are critical for its activation or its ability to bind to DNA.

Changes in the *STAT3* gene that cause AD-HIES alter the structure and function of the STAT3 protein, impairing its ability to control the activity of other genes. Because the mutations lead to impairment of the protein's normal function, they are called "loss-of-function" mutations. The lack of STAT3's signaling function disrupts the normal maturation of T cells (specifically a subset known as Th17 cells) and other immune system cells. The resulting immune system abnormalities make people with AD-HIES highly susceptible to infections, particularly bacterial and fungal infections

affecting the lungs and skin. Additionally, the role of STAT3 protein in the formation and maintenance of bone tissue may help explain why *STAT3* gene mutations lead to the skeletal and dental abnormalities characteristic of this condition.

prostate cancer

autoimmune disorders

At least 20 *STAT3* gene mutations have been found to cause a type of immune system abnormality known as an autoimmune disorder, in which the immune system malfunctions and attacks the body's own cells and tissues. In people with these mutations, autoimmunity typically begins in infancy or early childhood and involves more than one body system. Autoimmune disease in these individuals often results from immune system attacks on insulin producing cells in the pancreas (type 1 diabetes), red blood cells (autoimmune hemolytic anemia), platelets (autoimmune thrombocytopenia), or tissues in the digestive tract (autoimmune enteropathy). The mutations involved in this condition are typically inherited and are found in every cell of the body (known as germline mutations). They change single protein building blocks (amino acids) in the STAT3 protein, resulting in an altered protein that is abnormally active. Due to this effect, the mutations are classified as "gain-of-function."

Normally, the STAT3 protein is switched on and off in response to signals that control cell growth and development. A continuously active version of this protein relays messages to the nucleus even in the absence of these chemical signals. It is unclear how overactive STAT3 leads to dysregulation of the immune system and autoimmunity.

cancers

STAT3 gene mutations are found in approximately one-third of cases of a blood cancer called large granular lymphocytic leukemia (LGL), which is characterized by the accumulation of white blood cells (lymphocytes) that are abnormally large and contain structures called granules. Affected individuals may also have an autoimmune disorder, primarily rheumatoid arthritis or autoimmune hemolytic anemia, and other blood cell abnormalities, such as pure red cell aplasia. There are two forms of the condition, based on the type of white blood cell involved: T-cell large granular lymphocytic leukemia (T-LGL) and chronic lymphoproliferative disorders of NK cells (CLPD-NKs). Both forms have the same signs and symptoms.

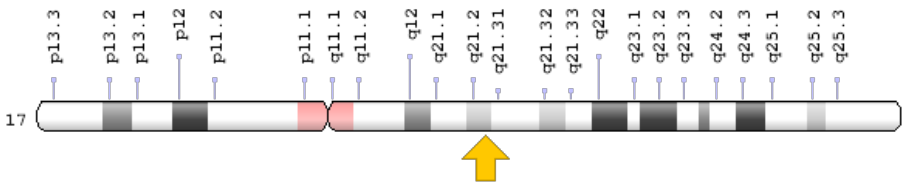
Unlike mutations that cause autoimmunity (described above), LGL-associated *STAT3* gene mutations are not inherited and are found only in the abnormal cells (known as somatic mutations). The mutations involved in LGL are classified as "gain-of-function," leading to an overactive STAT3 protein. Researchers believe that the overactive STAT3 protein instructs cells to continue growing and dividing, and prevents damaged cells from self-destructing (undergoing apoptosis). Excess STAT3

protein may contribute to the growth of cancers by allowing abnormal cells to grow and divide uncontrollably.

Chromosomal Location

Cytogenetic Location: 17q21.2, which is the long (q) arm of chromosome 17 at position 21.2

Molecular Location: base pairs 42,313,324 to 42,388,505 on chromosome 17 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- acute-phase response factor
- APRF
- APRF Transcription Factor
- DNA-binding protein APRF
- FLJ20882
- hypothetical protein MGC16063
- IL6-Response Factor
- LIF-Response Factor
- LIF(leukemia inhibitory factor)-Response Factor
- signal transducer and activator of transcription 3 (acute-phase response factor)
- STAT3_HUMAN

Additional Information & Resources

GeneReviews

- Autosomal Dominant Hyper IgE Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK25507

Genetic Testing Registry

- GTR: Genetic tests for STAT3
  https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=6774%5Bgeneid%5D

Scientific articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28STAT3%5BTI%5D%29+OR+%28signal+transducer+and+activator+of+transcription+3%5BTI%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+180+days%22%5Bdp%5D

OMIM

- SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3
  http://omim.org/entry/102582

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/STAT3ID444.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=STAT3%5Bgene%5D
- HGNC Gene Family: SH2 domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/741
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=11364
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/6774
- UniProt
  http://www.uniprot.org/uniprot/P40763

Sources for This Summary

- Frank DA. STAT3 as a central mediator of neoplastic cellular transformation. Cancer Lett. 2007 Jun 28;251(2):199-210. Epub 2006 Nov 28. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17129668
- Gao H, Ward PA. STAT3 and suppressor of cytokine signaling 3: potential targets in lung inflammatory responses. Expert Opin Ther Targets. 2007 Jul;11(7):869-80. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17614756

- Haapaniemi EM, Kaustio M, Rajala HL, van Adrichem AJ, Kainulainen L, Glumoff V, Doffinger R, Kuusanmäki H, Heiskanen-Kosma T, Trotta L, Chiang S, Kulmala P, Eldfors S, Katainen R, Siitonen S, Karjalainen-Lindsberg ML, Kovanen PE, Otonkoski T, Porkka K, Heiskanen K, Hänninen A, Bryceson YT, Uusitalo-Seppälä R, Saarela J, Seppänen M, Mustjoki S, Kere J. Autoimmunity, hypogammaglobulinemia, lymphoproliferation, and mycobacterial disease in patients with activating mutations in STAT3. Blood. 2015 Jan 22;125(4):639-48. doi: 10.1182/blood-2014-04-570101. Epub 2014 Oct 27.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25349174
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4304109/
- Hodge DR, Hurt EM, Farrar WL. The role of IL-6 and STAT3 in inflammation and cancer. Eur J Cancer. 2005 Nov;41(16):2502-12. Epub 2005 Sep 30. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16199153
- Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, Freeman AF, Demidowich A, Davis J, Turner ML, Anderson VL, Darnell DN, Welch PA, Kuhns DB, Frucht DM, Malech HL, Gallin JI, Kobayashi SD, Whitney AR, Voyich JM, Musser JM, Woellner C, Schäffer AA, Puck JM, Grimbacher B. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med. 2007 Oct 18;357(16): 1608-19. Epub 2007 Sep 19.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17881745
- Jerez A, Clemente MJ, Makishima H, Koskela H, Leblanc F, Peng Ng K, Olson T, Przychodzen B, Afable M, Gomez-Segui I, Guinta K, Durkin L, Hsi ED, McGraw K, Zhang D, Wlodarski MW, Porkka K, Sekeres MA, List A, Mustjoki S, Loughran TP, Maciejewski JP. STAT3 mutations unify the pathogenesis of chronic lymphoproliferative disorders of NK cells and T-cell large granular lymphocyte leukemia. Blood. 2012 Oct 11;120(15):3048-57. doi: 10.1182/blood-2012-06-435297. Epub 2012 Aug 2.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22859607
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3471515/
- Kane A, Deenick EK, Ma CS, Cook MC, Uzel G, Tangye SG. STAT3 is a central regulator of lymphocyte differentiation and function. Curr Opin Immunol. 2014 Jun;28:49-57. doi: 10.1016/ j.coi.2014.01.015. Epub 2014 Mar 6. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24594518
- Levy DE, Loomis CA. STAT3 signaling and the hyper-IgE syndrome. N Engl J Med. 2007 Oct 18; 357(16):1655-8. Epub 2007 Sep 19.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17881746
- Milner JD, Vogel TP, Forbes L, Ma CA, Stray-Pedersen A, Niemela JE, Lyons JJ, Engelhardt KR, Zhang Y, Topcagic N, Roberson ED, Matthews H, Verbsky JW, Dasu T, Vargas-Hernandez A, Varghese N, McClain KL, Karam LB, Nahmod K, Makedonas G, Mace EM, Sorte HS, Perminow G, Rao VK, O'Connell MP, Price S, Su HC, Butrick M, McElwee J, Hughes JD, Willet J, Swan D, Xu Y, Santibanez-Koref M, Slowik V, Dinwiddie DL, Ciaccio CE, Saunders CJ, Septer S, Kingsmore SF, White AJ, Cant AJ, Hambleton S, Cooper MA. Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function mutations. Blood. 2015 Jan 22;125(4):591-9. doi: 10.1182/blood-2014-09-602763. Epub 2014 Oct 30.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25359994
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4304103/
- Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, Kawamura N, Ariga T, Pasic S, Stojkovic O, Metin A, Karasuyama H. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature. 2007 Aug 30;448(7157):1058-62. Epub 2007 Aug 5.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17676033

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/STAT3

Reviewed: October 2015
Published: January 24, 2017

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services